Monoclonal antibody therapeutics: Leading companies to maximise sales and market share

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Abstract

A close look at the biology and pharmacology of monoclonal antibodies reveals both their continuing promise as therapeutic agents to address unmet medical needs, as well as a number of challenges to the future discovery and development of this unique class of biologics. A remarkably consistent experience of reliable clinical efficacy and safety ensures that Biotech and Pharma have strong incentives to accelerate the antibody drug discovery process. Their attractive commercial potential invites consideration of potential challenges to the future expansion of the monoclonal antibody drug market. Four challenges arise from scientific and technical aspects of the antibody drug format: drug target limitations, biodistribution limitations, species specificity issues, and limitations to the route of administration and four challenges are based in the commercial and clinical use of antibody drugs: cost of goods, product differentiation within the antibody market, competition from small molecule drugs, and price sensitivity of clinical acceptance. Despite these challenges and recent setbacks, such as the withdrawal and subsequent relaunch of Tysabri and the TGN1412 Phase I disaster, the prevailing opinion is that monoclonal antibodies will continue to be safe and effective medicines that are worthy of commercialisation.

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INTRODUCTION

The usage of immune horse antiserum to treat severe infectious diseases such as tetanus and diphtheria at the end of the 19th century was

the first application of therapeutic antibody drugs. Over a century of experience with biological drug products derived from human or animal serum followed, including polyclonal immunoglobulin antibodies to treat severe infections and snake bites, as well as the development of serum protein drug products to treat genetic or acquired deficiency diseases such as diabetes and haemophilia. This valuable knowledge base in the production, formulation, delivery, and clinical usage of serum-derived protein drugs set the stage for the rapid expansion of biotechnology-derived protein therapeutics beginning in the 1980s driven by advances in both recombinant DNA and monoclonal antibody technologies. These early years also previewed challenges that continue to impact the development of protein-based therapeutics including the formation of antibodies by patients that may neutralise the activity of a biological drug or trigger adverse reactions ranging from mild fever to life-threatening anaphylactic shock during repeated treatments.

Over two decades of the current biotechnology era has been characterised by intense research to develop antibody-based drugs beginning with the first clinical testing of mouse monoclonal antibodies. Now the industry standard has shifted away from non-human and chimaeric antibodies to focus on fully human or humanised antibody drug candidates. Significant advances in the discovery of human monoclonal antibody drug candidates have resulted in novel approaches utilising both *in vivo* and *in vitro* methods. *In vivo* approaches focus the power of the vertebrate adaptive immune system to directly create potent human antibodies in transgenic animals or non-human antibodies that are subsequently humanised. *In vitro* approaches are driven by advances in antibody library design[1] and these antibody libraries are subsequently used for selecting and increasing the affinity of human antibodies displayed on ribosomes, phage, bacteria, yeast, and mammalian cells derived from human B-cells. The potential of this accumulated technology is truly impressive, allowing the formation of polyclonal mixtures of fully human monoclonal antibodies with a thousand-fold improved potency and the potential to treat severe infectious diseases such as botulism.[2]

THE CURRENT ANTIBODY DRUG MARKET

The natural role of antibodies is to block infectious disease by binding foreign agents or infected cells leading to activation of the host immune system. Only one of the 21 current marketed drugs (Synagis, respiratory syncytial virus, MedImmune) and none of 38 advanced clinical antibody drug candidates, however, are designed for this type of application.[3] Some antibody drugs or drug candidates that target leukaemia, lymphoma, or severe autoimmune disease do bind to B-cell or T-cell-associated surface antigens (CD-20 or CD-52) in order to trigger depletion of their target cells by complement or Fcγ-receptor-mediated mechanisms; however, cell depletion by the immune system is not the goal of the majority of antibody therapeutics. Instead, the field has advanced by discoveries that create new functionalities for monoclonal antibodies, including receptor binding to modify activation, prevent dimerisation, trigger internalisation, block proliferation, or induce apoptosis, binding, and neutralisation of cytokines or growth factors, and targeting chemical, protein, or radioactive toxins to target cells. Largely as a result of the discovery of these and other novel functionalities, antibody drugs are now breakthrough therapies for a variety of diseases, especially in the area of oncology and severe immunological disease indications.

The current market size for monoclonal antibodies is estimated to be over $20bn (US). This market is dominated by five antibody drugs Avastin (bevacizumab), Herceptin (trastuzumab), Humira (adalimumab), Remicade (infliximab), and Rituxan (rituximab), which together account for ~80 per cent of market. In some estimates, the

antibody market is projected to grow to $30bn or even more over the next 3–6 years, driven mainly by oncology applications.[4,5] This growth will include a mixture of new therapeutic applications for marketed antibody drugs, improved antibodies aimed at clinically validated targets, and the introduction of novel antibody drugs to novel targets.

Recent trends indicate that large Biotech increasingly relies on an ageing portfolio of approved protein therapeutics;[6] therefore, these projected market increases may need to be adjusted if the rate of successful launches leading to novel antibody drugs begins to slow. Biotech and Pharma, however, have a compelling incentive to accelerate the antibody drug discovery process because the commercial aspects of this drug modality remain very impressive. Therapeutic antibodies have a high drug approval success rate once they reach clinical testing (29 per cent for chimaeric antibodies, 25 per cent for humanised antibodies compared to a success rate of approximately 11 per cent for small molecules).[7] In addition, much of the development and clinical experience that is gained from the generation and optimisation of one antibody product can be readily applied to subsequent therapeutic antibodies, diminishing some of the development, manufacturing, and clinical risks that are intrinsic to drug development.

Owing to their exquisite specificity and ability to affect unique biological functions, monoclonal antibodies have the potential to provide a continued source of effective, safe, and reliable therapies. The introduction of such new therapies will benefit patients having a variety of debilitating diseases that otherwise respond poorly to alternate approaches. Based on the impact of the successful discovery of novel antibody functions on the current portfolio of antibody drugs, it is likely that the ability to continue to engineer novel functionalities by using new antibody formats will drive the expansion of the antibody drug market in the future.

POTENTIAL CHALLENGES TO THE FUTURE OF ANTIBODY DRUGS

The discovery of a continued stream of monoclonal antibody-based therapies offers tremendous opportunities for Pharma and Biotech companies, but also harbours a variety of scientific and commercial challenges. Currently, 21 monoclonal antibodies are approved for therapeutic use, 11 of which are humanised, five chimaeric, three of murine origin, while only two are fully human antibodies. In contrast, of 38 antibodies in advanced clinical testing, 31 are either humanised (14) or fully human (17). These numbers confirm that human antibodies are now the standard of the industry, whether obtained by *in vivo* (immunisation) or *in vitro* (antibody display) methods. Given the large number of antibodies in clinical trials or preclinical development, it is clear that technologies for the discovery of human antibodies are not rate limiting. Rather, the key to success will either be to identify the most effective, novel, and proprietary target in a complex pathological setting, or to identify a more effective approach to a known target, and both will be guided by emerging target validation approaches.

It is instructive to consider eight challenges to the future expansion of the monoclonal antibody drug market. Four of these challenges arise from scientific and technical aspects of the antibody drug format: drug target limitations, biodistribution limitations, species specificity issues, and limitations to the route of administration. The remaining four challenges arise from a consideration of the commercial and clinical usage of antibody drugs: cost of goods, product differentiation within the antibody market, competition from small molecule drugs, and price sensitivity of clinical acceptance.

Drug target limitations

Following intravenous injection, antibody drugs access targets in the extracellular and vascular

space. The Fc domain of the IgG format interacts with the endothelial FcRn receptor, facilitating access to the perivascular space after transient movement through the endothelium; however, the interior of these endothelial cells is not targeted. Antibody immunotoxin conjugates utilise antibody internalisation following receptor binding, but the goal of this application is delivery of the toxin payload to the intracellular space, not delivery of the antibody itself, which is rapidly hydrolysed. Disulphides that are needed to maintain the dimeric structure of the IgG format break down in the reducing environment of the intracellular cytosol and deactivate the potent binding of the antibody. Thus, antibody drugs are limited to extracellular targets.

The consequence of this limitation can be appreciated by considering the rich list of intracellular drug targets, several of which are targeted by small molecule drugs that are market leaders. These intracellular targets include HMG-CoA reductase (statins), nuclear hormone receptor agonists or antagonists (glucocorticoid, oestrogen, progesterone, etc), phosphodiesterase (PDE5), immunophilins (cyclosporine, FK506), and kinases (receptor tyrosine kinase, thymidine kinase). Even when limited to the extracellular arena, there appears to be a preference for prominent antigens on extracellular domains or soluble ligand targets. Thus, a notable omission from the list of extracellular targets that have been addressed by advanced antibody candidates include the seven-transmembrane receptors. In this large and ubiquitous family of membrane receptors are the G-protein coupled receptors (GPCR) that are often therapeutic targets for small molecule drugs. Technical advances may expand the range of extracellular targets for antibody drugs to include the GPCRs; however, it is not likely that the natural limitations of antibodies will be overcome to allow access to valuable intracellular targets.

Biodistribution limitations

Significant biodistribution and tissue penetration challenges limit the application of antibody drugs. Solid tumours make up the majority of human cancers (~85 per cent). To date, nine antibodies have been approved for the treatment of human cancers, but only three target solid tumours and one of these, bevacizumab, is actually directed towards a soluble ligand target, not to its cell surface receptor expressed on cells inside the solid tumour tissue. This suggests that additional barriers are associated with the treatment of solid tumours that are not present for haematological malignancies. These limitations need to be addressed before the successful treatment of human solid tumours by antibody drugs can expand. Even greater challenges may exist for other disease indications in privileged tissue like the central nervous system. When faced with these challenging biodistribution applications, the high-molecular-weight IgG format may ultimately fail to achieve the required tissue penetration. In the future, this natural antibody format may be replaced by protein drugs derived from alternate antibody formats or antibody mimetic scaffolds. It remains to be determined whether these molecules are able to more effectively access poorly vascularised tumours or tissues protected by the blood–brain barrier.

Species specificity issues

One of the valuable properties of antibody drugs is their exquisite specificity, allowing them to bind one particular epitope in the presence of many other similar binding targets. This may, however, lead to extended preclinical development times for antibody drugs because antibodies to a human target may not bind the similar target molecule in species commonly used for efficacy or safety testing (mouse, rat, rabbit, dog, etc). In addition, well-known recent clinical results indicate that the species specificity of Fc receptor binding must be given greater consideration during development of future antibody drugs.

There is not one universally accepted solution to the issue of species specificity of

antibody epitope recognition; however, there are a number of potential solutions, all of which add time or require significantly more resources for antibody drug discovery. One potential solution is to develop two separate antibodies in parallel in order to include one antibody that recognises the antigen in a species used for animal testing. Another solution is to establish transgenic mice expressing both the human target protein and the necessary human auxiliary proteins in order to allow testing of human-specific antibodies in transgenic mouse models. A third potential solution is to screen antibodies that recognise both the human and the mouse antigen and advance only those candidate antibodies with dual species specificity. This option harbours the potential risk of discarding unique antibodies to a functional human epitope not found on the mouse homologue. A final potential option would be to complete the entire concept validation studies *in vitro* utilising human cell or tissue-based models. Then, the first *in vivo* proof of concept would be in human clinical studies; however, the acceptance of this approach is problematic in the post-TGN1412 era.

The major lesson arising from the disastrous clinical testing of TGN1412 (anti-CD28 IgG T cell superagonist) is that special caution is needed in the design and execution of 'first in man' clinical trials.[8] In addition, however, based on this tragic event, an increased emphasis on preclinical consideration of Fc receptor interactions is likely to be required by regulatory agencies.[9] The 'cytokine storm' was not found during preclinical testing of TGN1412 in cynomolgus monkeys, indicating that species differences in Fc receptor binding may be important for IgG tests even in non-human primates. Functional aspects of the traditional IgG format can be finely tuned by post-translational glycosylation in a proprietary production cell line or by Fc engineering to selectively trigger effector functions such as antibody-dependent cellular cytotoxicity. It is clear that the Fc portion of the monoclonal antibody plays a significant role in the extended serum half-life that is now expected for this class of biological drugs. Thus, Fc modifications must achieve the right balance of clearance, Fc receptor functionality, and clinical safety. Modification or elimination of Fc receptor binding altogether may be included as a motivation to pursue alternatives to the traditional IgG format. Various new antibody formats as well as mimetics are being pursued, but there is limited or no clinical experience with most of these antibody formats and mimetics. The jury is still out on whether one of the many emerging novel scaffolds that eliminate Fc receptor binding can effectively substitute for monoclonal antibodies in the mid-term. It is likely, however, that preclinical development issues based on species-specific target recognition will continue to challenge both antibody and antibody mimetic-based drug candidates.

Limitations to the route of administration

Four of the top five selling antibody drugs and 16 of the 21 approved antibody drugs are administered by intravenous infusion. Several antibody drugs are approved for subcutaneous injection. Selected antibodies either are approved or have been successfully tested in the clinic using other routes of administration often designed for a specific indication including intramuscular (palivizumab), intravitreal (ranibizumab), intracoronary (abciximab), and intraperitoneal, intraventricular, or intralesional (rituximab). Subcutaneous injection offers the possibility of self-injection by the patient; however, a comparison of the TNFα antagonists infliximab (intravenous infusion) and adalimumab (subcutaneous injection) showed equivalent short-term efficacy despite this difference in the route of administration.[10] Over the course of long-term treatment, self-administration and ease of use may be anticipated to impact patient compliance and acceptance of antibody drugs. Insulin represents a protein therapeutic that is readily

delivered by subcutaneous injection, but over the years more acceptable delivery methods have been actively sought due to market demand. In the case of insulin, both the popular insulin pen technologies utilising extremely small, short needles as well as inhaled insulin powder (Exubera) have subsequently been developed. When the relatively low molecular weight of insulin (~5,800 Da) is compared to the high molecular weight of the IgG format (~150,000 Da) found in the majority of approved antibody drugs, it is clear that further technical advances will be needed to achieve the ease of use of pen injection or inhalation technologies. An additional potential benefit of the lower molecular weight of either alternate antibody formats (~25,000–75,000 Da) or antibody mimetics (~9,000–15,000 Da) may be to allow expanded routes of administration. If any of these improved routes of administration are realised they will represent an important milestone for the development of these alternatives to traditional antibody drugs.

Cost of goods (COGS)

Significant costs are associated with the identification, optimisation, and production of monoclonal antibodies due to the cost of manufacturing and intellectual property considerations. Because of their complex structure, monoclonal antibodies in the IgG format are generally limited to production in mammalian cells. These large protein drugs (~150,000 Da) require post-translational modifications and critical disulphide bonds for full activity. The usual route of production in either Chinese hamster ovary (CHO) or mouse myeloma (NS0) cell lines is often expensive and time consuming. The technologies to discover and produce monoclonal antibodies have been heavily patented and companies that are active in this field often need to acquire one or more licenses, either research or commercial. These intellectual property costs are not associated with a single patent and not limited to the antibody molecule itself, but may include a collection of technologies needed for antibody drug generation, optimisation, and production. These technologies may include, among others, affinity maturation, humanisation methods, the expression systems (promoter and poly A sequence), and cell lines used to produce the antibody with the appropriate post-translational modifications needed to ensure the desired functionality. The cumulative costs associated with licensing these technologies are often referred to as 'stacking royalty' payments.

Product differentiation within the antibody market

Within the TNFα antagonist arena, different routes of administration have not yet distinguished similar antibody products with respect to short-term efficacy. This indication is not unique in having several approved antibody drugs or antibody drug candidates in advanced development. Marketed antibody drugs and advanced candidates are often directed to the same target and there are apparently four TNFα antagonists (infliximab, adalimumab, golimumab, certolizumab) in addition to the Fc fusion protein etanercept, five antibodies targeting the B cell receptor CD20 (rituximab, ibritumomab, tositumomab, ofatumumab, ocrelizumab), five to the EGF receptor EGFR (cetuximab, panitumumab, matuzumab, nimotuzumab, zalatumumab), and three to VEGF/VEGFR signalling (bevacizumab, ranibizumab, CDP-791) in addition to the Fc fusion VEGF-Trap. A simple list is not a fair comparison and in some cases the antibody formats are different (immunotoxin versus naked antibody, or IgG versus Fab), the indications are different (solid tumour versus macular degeneration, lymphoma versus arthritis), or the approach to the target is different (soluble ligand versus receptor extracellular domain); however, it is clear that the potential to differentiate between similar antibody products will represent a challenge to the industry.

Competition from small molecule drugs

In addition to the need to differentiate antibody drugs from each other, there is emerging pressure from small molecule drugs directed toward similar targets as the antibodies. No good solution has been found to the daunting technical challenge of finding small molecules that can bind and block tight protein–protein interactions. Antibodies are excellent agents for binding one protein and preventing binding of its biological partner. Small molecule drugs are not likely to compete directly with antibodies using this mechanism, but the therapeutic targets of antibody drugs may be addressed by alternate mechanisms taking advantage of the ability of small molecule drugs to antagonise intracellular targets. Growth factor receptors often are comprised of an extracellular domain suitable for antibody binding and an intracellular kinase domain that may be antagonised by small molecule inhibitors. Lapatinib (Glaxo Smith Kline) is an example of one such oral receptor tyrosine kinase inhibitor that targets both EGFR (ErbB-1) and HER2 (ErbB-2) receptors and that may compare favourably with antibody drugs to these targets. Similarly, by inhibiting the tyrosine kinase domains of VEGFR-1, VEGFR-2, and VEGFR-3 and other receptors (Raf, PDGFR-B, KIT, FLT-3, and RET), the oral drug Nexavar (Bayer) may compare favourably to antibodies targeting VEGF/VEGFR signalling. In the future, combined treatment that includes both antibody and small molecule drugs may prove most effective for life-threatening diseases. It is likely, however, that further challenges to the ability of antibodies to address drug targets will arise from advances in the ability to identify small molecule leads to the same targets.

Price sensitivity of clinical acceptance

The cost issues for antibody therapies do not end when the antibody drug has been successfully produced and packaged. Antibody drugs targeting cancer rarely cure this disease, especially in the advanced stages of cancer. For maximum benefit, antibody cancer drugs are usually administered in combination with chemotherapy or radiotherapy. These combined treatments significantly increase the total cost to the patient. For example, the FOLFOX regimen (Fluorouracil, leucovorin, and oxaliplatin) costs nearly $12,000 dollars for an 8-week course compared to approximately $21,000 for FOLFOX combined with the antibody drug bevacizumab, but the combination with antibody drug results in a significant increased benefit in the median survival time.[11] Improved benefits in the clinic will drive Biotech and Pharma to work with clinicians to find ways to continue to improve the costs of antibody therapies. National healthcare providers, however, may be reluctant to pay for the high cost of antibody drugs. Recently, the National Institute for Health and Clinical Excellence in the United Kingdom was widely criticised when it failed to recommend cetuximab and bevacizumab for advanced bowel cancer based on their estimate that these drugs were not cost-effective in the treatment of metastatic colorectal cancer.[12] Thus, a final challenge will be to identify antibody drugs that are efficacious therapeutics and that are recognised as cost-effective by healthcare providers.

In summary, monoclonal antibodies, along with their derivatives and conjugates, provide tremendous opportunity in the mid-term for the discovery of new treatments for diseases with high unmet medical need. Despite recent setbacks such as the withdrawal and subsequent relaunch of Tysabri and the TGN1412 Phase I disaster, the prevailing opinion is that monoclonal antibodies will continue to be safe and effective medicines. Emerging technologies in novel antibody formats and mimetics will further provide opportunities to improve this unique class of biological drugs and will help to ensure their continued commercial success.

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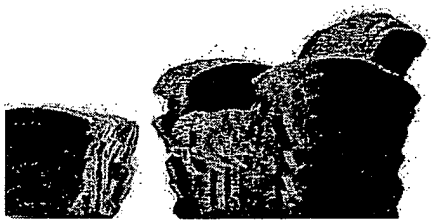
FROM THE ANALYST'S COUCH

Monoclonal antibodies market

Janice Reichert and Alex Pavlou



'Little Beaver', designed by Frank O'Gehry, from Vitra.com (photographer Hans Hansen)

Following the success of recombinant proteins, therapeutic monoclonal antibodies (mAbs) represent the second wave of innovation created by the biotechnology industry during the past twenty years. Between 2001 and 2002, the value of the global therapeutic mAb market grew by 37% to US $5.4 billion. Chimeric mAbs were the undisputed leaders, with 43% growth and US $3.8 billion in sales, followed by humanized mAbs with more than US $1.4 billion in sales and growth of 29%. The current global clinical antibody pipeline, which comprises 132 products in development and is dominated by humanized (42%) and fully human (28%) mAbs, is poised to deliver as many as 16 new products between 2004 and 2008. As a result of growth in existing markets for mAb therapeutics, and the opening of new ones, the global market is projected to increase to US $16.7 billion in 2008.

mAbs approved for marketing

To date, 17 therapeutic mAbs, comprising four different types, have been approved by the US FDA: three murine, five chimeric, eight humanized and one human. Nine of the seventeen mAbs have also been approved in the European Union (EU). All of these products were approved in the United States first, though all were approved in the EU within two years of the US approval date. Mean approval times for mAbs are faster in the United States compared with the EU because the FDA has given priority review designation to a majority of the marketing applications. Of the approved products, the best-seller is Johnson & Johnson/Schering-Plough's infliximab (Remicade), with sales of US $1.6 billion, representing 30.5% of the total market sales in 2002. This product was also the fastest-growing product in 2002, with sales increasing by 84%.

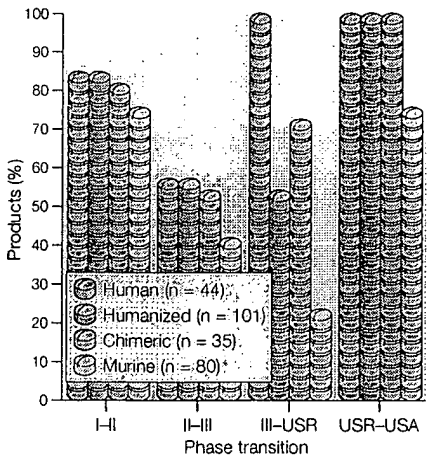


Figure 1 | **Phase transition probabilities* for four types of therapeutic mAbs.** *Phase transition probabilities were calculated as follows: the number of products that completed a given phase (for example, Phase I) and entered the next (for example, Phase II) was divided by the difference between the number of products that entered the phase and those that were still in the phase at the time of the calculation. Clinical studies for human antibodies initiated during 1994 to 2003. Source: Tufts Center for the Study of Drug Development. USA, US approval; USR, US review.

Advancing to the next phase

Although many products might start on the path to approval, not all will complete the convoluted process. In our analysis, probabilities of product advancement from the start of clinical development through US approval were calculated on the basis of current development status of 260 products identified as either murine, chimeric, humanized or human mAbs (FIG. 1). Murine mAbs had the lowest transition probabilities at each phase. The chimeric, humanized and human products had similar Phase I to II and Phase II to III transition probabilities, but the probabilities diverged at the Phase III to US review transition. For the vast majority of mAb products, if the FDA filed the marketing application, then the product ultimately received approval.

Measure of success

Approval success rates are a measure of the likelihood of receiving marketing approval for a product that enters clinical testing. The range of overall approval success for the four types of mAbs was large. To date, the murine products have been least successful (4.5%), whereas the chimeric mAbs have been most successful (26%). The approval success rates for the humanized (18%) and human (14%) mAbs were in the middle of the range. The majority of the humanized and human mAbs are still in clinical development, so the approval success rates might change as the fate of more products is determined. Additional variation in the success rates was observed when the mAbs were categorized by both type and therapeutic category. For example, the success rates for antineoplastic and immunological chimeric mAbs were 29%, whereas humanized antineoplastic and immunological mAbs had a 25% and 17% success rate, respectively.

Waves of the future

Looking toward the future, we anticipate two major approval waves during the next five years. The first will occur between 2004 and 2006, with humanized antibodies comprising the largest number of approvals, whereas the second will occur between 2007 and 2008, and be dominated by human antibody products. Of particular interest, Osidem (ImmunoDesigned Molecules), a combination of a bispecific mAb and macrophage-activated killer cells, and two radiolabelled antibodies might reach the market by 2008. One product produced using a novel engineering approach, Celltech's fragmented antibody CDP-870, is expected to launch in 2006.

A growing market

Although growth will rely on the rise of humanized and human antibodies, chimerics, led by infliximab and rituximab (Rituxan; Genentech), will dominate with a 49% market share in 2008. Humanized antibodies will follow, with sales forecast to reach US $5.2 billion, or a 31% market share by 2008. In addition, fully human antibodies with 2008 sales of US $1.9 billion, will capture 11% of the market in 2008.

Two therapeutic categories — oncology and arthritis, immune and inflammatory disorders (AIID) — will likely be the commercial and research focus during the next four years. With the recent approvals of cetuximab (Erbitux; Imclone Systems) and bevacizumab (Avastin; Genentech), oncology will be the leading income earner, with forecast sales of US $7.2 billion in 2008, representing a 43% market share. Meanwhile, AIID sales will almost quadruple from US $1.7 billion to $6.7 billion in 2008, or a 40% market share. In addition, the industry might see approvals in new areas such as the 2005 launch of the humanized antibody natalizumab (Antegren; Biogen IDEC/Elan) for the treatment of multiple sclerosis. ▶

MONOCLONAL ANTIBODIES MARKET | **MARKET INDICATORS**

▶ The antibody-focused biotechnology industry has garnered US marketing approval for 13 therapeutic mAbs during the past six years (TABLE 1). During the next five years, the industry has the potential to double the number of approved mAbs, and can anticipate a tripling of the global market for mAb products (see FIGS 2,3). To achieve this result, the industry needs to continue to evolve towards technology integration and market expansion. Success will depend on strategies targeting shorter development times, higher success rates, innovative molecular engineering, robust intellectual property protection and the development of cost-effective manufacturing.

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Online links

FURTHER INFORMATION
US Food and Drug Administration: http://www.fda.gov
European Agency for the Evaluation of Medicinal Products: http://www.emea.eu.int
Access to this interactive links box is free online.

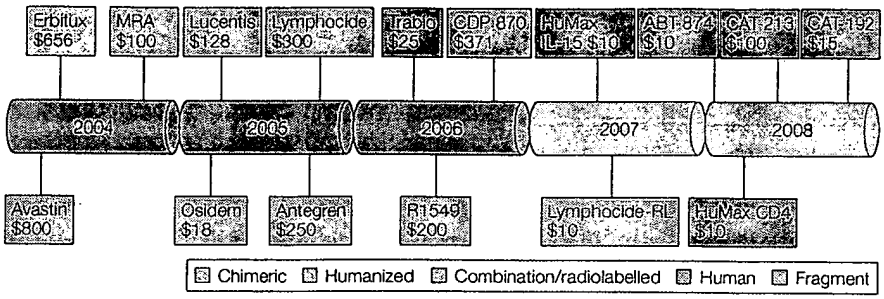

Figure 2 | **New product approval trajectories in terms of technological exposure and sales potential in 2008.** Sixteen new antibodies are expected to reach the market over the next four years. Amounts in US $ millions. Source: Datamonitor. IL, interleukin; MRA, humanized anti-human IL-6 receptor monoclonal antibody.

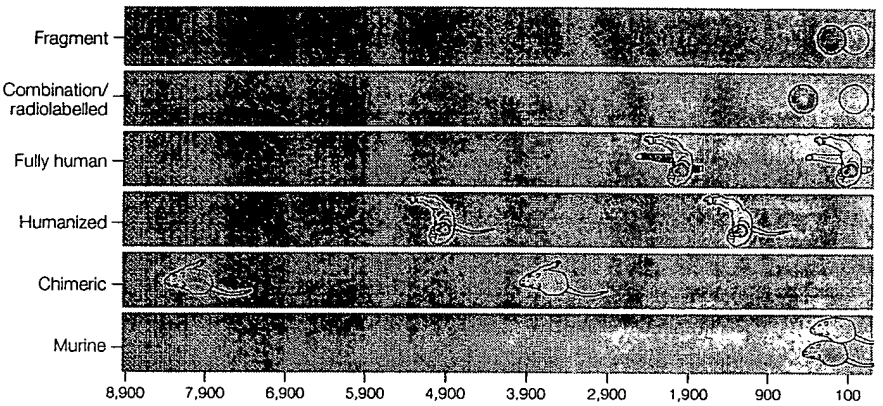

Figure 3 | **Comparison of therapeutic mAb sales trajectories in 2002 (yellow) and 2008 (blue) in terms of technological focus.** Despite the undisputed leadership of chimeric mAbs, the contribution of humanized and fully human products to total market size will significantly rise. Source: Datamonitor.

Table 1 | **Therapeutic mAbs approved in the United States and European Union**

Sponsor company	Generic name	US trade name	mAb type	Therapeutic category	US approval date	EU* approval date
Johnson & Johnson	Muromonab-CD3	Orthoclone OKT3	Murine	Immunological†	19.06.1986	NA
Centocor	Abciximab	ReoPro	Chimeric	Hemostasis	22.12.1994	NA
Biogen IDEC	Rituximab	Rituxan	Chimeric	Antineoplastic	26.11.1997	02.06.1998
Protein Design Labs	Daclizumab	Zenapax	Humanized	Immunological	10.12.1997	26.02.1999
Novartis	Basiliximab	Simulect	Chimeric	Immunological	12.05.1998	09.10.1998
MedImmune	Palivizumab	Synagis	Humanized	Anti-infective	19.06.1998	13.08.1999
Centocor	Infliximab	Remicade	Chimeric	Immunological	24.08.1998	13.08.1999
Genentech	Trastuzumab	Herceptin	Humanized	Antineoplastic	25.09.1998	28.08.2000
Wyeth	Gemtuzumab ozogamicin	Mylotarg	Humanized	Antineoplastic	17.05.2000	NA
Millennium/ILEX	Alemtuzumab	Campath	Humanized	Antineoplastic	07.05.2001	06.07.2001
Biogen IDEC	Ibritumomab tiuxetan	Zevalin	Murine	Antineoplastic	19.02.2002	16.01.2004
Abbott	Adalimumab	Humira	Human	Immunological	31.12.2002	08.09.2003
Genentech	Omalizumab	Xolair	Humanized	Immunological	20.06.2003	NA
Corixa	Tositumomab-I131	BEXXAR	Murine	Antineoplastic	27.06.2003	NA
Genentech	Efalizumab	Raptiva	Humanized	Immunological	27.10.2003	NA
Imclone Systems	Cetuximab	Erbitux	Chimeric	Antineoplastic	12.02.2004	NA
Genentech	Bevacizumab	Avastin	Humanized	Antineoplastic	26.02.2004	NA

*Approved using EU centralized procedure. †Includes arthritis, immune and inflammatory disorders and prevention/reversal of transplant rejection; NA, not approved. Source: Tufts Center for the Study of Drug Development.

Enablement in Claims to Therapeutic Treatment

Jean Witz
tQAS, TC1600

35 U.S.C. § 112, 1st Paragraph

- Specification must teach how to make and use the invention
- Is the experimentation needed to practice the invention undue or unreasonable?

Therapeutic Treatment

- **Inquiry may involve**
  - **How to use the claimed invention**
  - **How to make the claimed invention**
- **Method claims reciting therapeutic treatment**
- **Composition or compound claims reciting intended therapeutic use**

35 U.S.C. § 112, 1st Paragraph

- The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art

- However, even in unpredictable arts, a disclosure of every operable species is not required

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- In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)
- Examiner is the fact finder
- All evidence must be weighed by the examiner
- No per se rules
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- The examiner has the initial burden to establish a reasonable basis to question the enablement provided for the either the full scope or a part thereof of the claimed invention
- There must be a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support

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- References should be supplied if possible to support a prima facie case of lack of enablement, but are not always required
- Specific technical reasons are always required

State of the Art

- Whether or not experimentation is routine depends on what is well-known in the art at the time of filing
- Enablement analysis is performed based on the state of the art combined with any evidence presented in the specification

State of the Art

- An applicant may omit from the disclosure any routine technology that is well known at the time of application

Therapeutic Methods/Uses

- **Is there any unpredictability in the scope of the claimed therapeutic method and has this unpredictability been resolved by evidence presented in the specification?**

In re Gardner, 427 F.2d 786, 166 USPQ 138 (C.C.P.A. 1970)

- Claim to a pharmaceutical composition comprising 2-aminomethyl-1,3-benzodioxole compounds having antidepressant activity
- "In effect, by [claiming therapeutic activity, applicants] are claiming in terms of use. It behooves them, therefore, to disclose how to use, as section 112 ordains . . . ."

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- **Appellants, relying on an affidavit, argue**
  - **efficacy in a rat model correlated to antidepressant activity in man**
  - **that the proper dosage would have been within the skill of a pharmacologist**

Highlights and Guidance

- The lack of direction provided by the inventor and the lack of working examples appeared to be the factors weighed most heavily by the court
- The enablement of compositions reciting activity or intended use must be considered

In re Jolles, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980)

- Methods of treating acute myeloblastic leukemia in humans comprising administration of naphthacene derivatives
- Pharmaceutical compositions for treatment of acute myeloblastic leukemia comprising naphthacene derivatives

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  - Claimed derivatives had a close structural relation to daunorubicin and doxorubicin
- **Two declarations**
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  - Provided no documentary evidence
- **The Board**
  - Affirmed the Examiner
  - Provided no documentary evidence

In re Jolles, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980)

- **The Court**
  - noted that neither the solicitor nor the examiner provided support for the assertion regarding "incredible utility"
  - held that Board erred by failing to give sufficient weight to the similarity of the remaining claimed derivatives to the allowed derivative
  - This similarity combined with the close structural relationship to known anti-neoplastic agents would have enabled the method/use

Highlights and Guidance

- The state of the prior art, the amount of direction provided by the inventor as well as the declaration evidence outweighed the Examiner's unsupported allegations
- A finding of lack of enablement must be based on evidence

In re Bundy, 642 F.2d 430, 209 USPQ 48 (C.C.P.A. 1981)

- Claims to prostaglandin E analogs
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- **Court held that**
  - **The evidence of change in pharmacologic activity was related to PGF, not PGE**
  - **The discussion of PGE related only to a matter of degree of potency**
  - **The result in Gardener was distinguished due to claims to compounds without recitation of use**

Highlights and Guidance

- Claims to compounds or compositions that do not recite an intended use need only one enabled use
- Evidence of unpredictability must be sufficiently related to the claimed invention

Glaxo v. Teva, 2004 WL 1875017 (D. Del. 2004)

- Glaxo patents with claims to a method of treatment for the relief of nausea and vomiting comprising the administration of ondansetron
- As one of the defenses to an action for infringement, Teva asserted lack of enablement of a priority document

Glaxo v. Teva, 2004 WL 1875017 (D. Del. 2004)

- Teva argued the absence of working examples in the priority document
- The priority document
  - Identifies ondansetron specifically
  - Teaches its use as anti-emetic
  - Provides a dosage range
  - Provides routes of administration

Glaxo v. Teva, 2004 WL 1875017 (D. Del. 2004)

- Court finds
  - no requirement in the law for working examples
  - priority document clear on its face
  - Teva bore the burden of providing clear and convincing evidence of lack of enablement and failed to do so

Highlights and Guidance

- **Lack of working examples alone is insufficient to support a finding of lack of enablement**
- **The absence of working examples may be probative where the evidence indicates unpredictability that may need to be resolved by exemplary evidence**

Rasmussen v. SmithKline, 413 F.3d 1318, 75 USPQ2d 1297 (Fed. Cir. 2005)

- Interference appeal
- Rasmussen lost interference to SmithKline
- Claims to methods of treating prostate cancer by administration of a 5aR-inhibiting compound, specifically finasteride

Rasmussen v. SmithKline, 413 F.3d 1318, 75 USPQ2d 1297 (Fed. Cir. 2005)

- **The Board held that Rasmussen's priority document failed to enable the claimed invention in view of**
  - **The state of the art**
  - **The lack of data to demonstrate the effects of finasteride in treating prostate cancer**

Rasmussen v. SmithKline, 413 F.3d 1318, 75 USPQ2d 1297 (Fed. Cir. 2005)

- **On appeal, Rasmussen argues that**
  - **The Board's findings regarding lack of a showing of efficacy are not relevant to a finding of lack of enablement, but pertains only to utility**
  - **The enablement requirement of Section 112 does not mandate a showing of utility and if it does, the requirement mandates only a showing that it is "not implausible" that the invention will work for its intended purpose**

Rasmussen v. SmithKline, 413 F.3d 1318, 75 USPQ2d 1297 (Fed. Cir. 2005)

- **The court disagrees, holding**
  - **Failure to disclose "how to use" may support a rejection under 35 USC 112, 1st paragraph**
  - **"[I]t is proper for the examiner to ask for substantiating evidence unless one with ordinary skill in the art would accept the allegations as obviously correct."**

Highlights and Guidance

- The unpredictability in the state of the art and the level of skill was unresolved by the Appellant
- Evidence of unpredictability in the art in the absence of data that resolves the unpredictability is often the basis for a conclusion of lack of enablement

Impax v. Aventis, 496 F.Supp.2d 428 (D. Del. 2007)

- Claims to method of treating ALS by administering riluzole
- Impax asserted invalidity based on prior art anticipation of Aventis patent
- Aventis argued asserted prior art was not enabling

Impax v. Aventis, 392 F.Supp.2d 428 (D. Del. 2007)

- **Aventis asserted that the patent**
  - **discloses thousands of formula I compounds and numerous diseases, yielding thousands of possible combinations**
  - **provides no direction or guidance to arrive at the claimed invention of using riluzole to treat ALS**
  - **does not disclose any working examples of the claimed invention**

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- Impax asserted that the patent
  - includes riluzole as a formula I compound
  - suggests that formula I compounds may be used to treat ALS
  - provides some dosage information

Impax v. Aventis, 392 F.Supp.2d 428 (D. Del. 2007)

- **Impax directs the Court to information contained in the patent to suggest that undue experimentation would not be required**
  - **In human therapy, the compounds according to the invention are especially useful in the treatment and prevention of convulsive phenomena, schizophrenic disorders, and in particular the deficiency forms of schizophrenia, sleep disorders, phenomena linked to cerebral ischaemia and also neurological conditions in which glutamate may be implicated, such as Alzehimer's disease, Huntington's chorea, amyotrophic lateral sclerosis and olivopontocerebellar atrophy**

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- **The District Court finds**
  - **"the compounds of the claimed invention are associated with the treatment of at least 8 different diseases, and there is nothing in the patent which would lead one to recognize that any specific compound, let alone riluzole, would be used to treat any specific disease, let alone ALS."**
  - **that the mere mention of riluzole was insufficient to put one skilled in the art in the possession of the claimed invention as is required to support a conclusion of enablement**

Highlights and Guidance

- **Specification detailing extensive lists of conditions to be treated and compounds to be used, yielding large numbers of possible combinations may suggest lack of enablement of claim to specific combination in the absence of working examples and if evidence of unpredictability exists in the prior art**

Pharmaceutical Resources v. Roxane Laboratories, Inc., 2007 WL 3151692 (Fed. Cir. 2007)

- Non-precedential Fed. Cir. opinion affirming the District Court finding that Par's patents were invalid for lack of enablement
- Claims to oral pharmaceutical composition of megestrol acetate, choices of specific alcohols and a surfactant

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- Claim language did not limit type or amount of surfactant
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- The court held the claims lacked enablement based, in part, on evidence of unpredictability provided previously by Par
- The court also considered the breadth of the claims, the presence of working examples and unsupported conclusions in declarations

Highlights and Guidance

- **Evidence of unpredictability presented to support a conclusion of nonobviousness may be then appropriate to support a finding of lack of enablement for at least a portion of the scope of the claim**

Review

- **Enablement analysis of therapeutic treatment claims begins with the claims by determining breadth of the claims with regard to**
  - **The condition to be treated**
  - **The compound/composition administered**

Review

- **Enablement analysis of therapeutic treatment claims continues with determination of the presence of any unpredictability within the state of the art with regard to**
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Review

- **Enablement analysis of therapeutic treatment claims finishes with the specification by evaluation of**
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Review

- **Evidence of unpredictability or predictability may occur in the**
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Highlights and Guidance

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Thank You!

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